REM and Remembering: The Nature of Memory Consolidation and Memory Retrieval

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"Many animals have memory and are capable of instruction, but no other animal except man can recall the past at will" – Aristotle

1. Introduction

1.1 Memory – A window into the past

Memories are experiences common to all of us that provide us with glimpses of the past. The phenomenon of having a memory is usually ascribed (scientifically) to activity of the brain. Memories are thought to be stored in our brains and are retrieved at later times. If the present is the temporal range within which we move through life and experience reality, then memories are the phenomenological expression of how we experienced the past.

The primary aim of the following essay is to investigate the nature of this vague concept humans have of the past that is referred to as memory. The mechanisms that are involved in the storage, or consolidation of memories and the processes involved in memory retrieval will be discussed. Specifically, an effort will be made to determine whether memories are retrieved in a distributed fashion (from several areas of the cortex at once), or are they retrieved in a local manner (from a specific region of the cortex where a memory is stored)? To achieve this end, memory will first be considered in a very broad fashion, then we will turn to a discussion on the anatomy of memory formation, and finally our discussion will be siphoned down to a possible way with which to investigate the nature of memory retrieval.

1.2 Sleep and memory – Causal relationship or correlational?

The secondary aim of this essay will center around the role of REM sleep in the formation and consolidation of memory. There is a significant amount of research dedicated to this subject (to be discussed

below) much of which claims that the purpose of REM sleep is the consolidation of newly formed memories. This will be contested by a comparative review of sleep patterns across several mammalian species. The chemistry and neurophysiology of sleep will be detailed to reinforce the assertion that sleep is correlational with memory retrieval but not causally related.

Sleep as expressed in several mammalian species, such as the bottlenose dolphin will be analyzed, and the implications of some unique sleep patterns found within these animals will lead this discussion to some queries regarding the primary aim of the paper – ascertaining if memory is retrieved in a localized or distributed fashion. A research proposal will be made that attempts to address these questions by inducing a conscious state in primates similar to the patterns expressed in dolphins, and by subsequently testing a primate using an interval timing paradigm.

Possible outcomes will be considered, as well as their implications regarding the nature of memory retrieval. Concluding remarks will center on a possible evolutionary role for sleep. Finally, a speculative digression concerning the possibility that, if alternative mechanisms could be induced that mimicked the biological function of sleep, it is theoretically conceivable that the human being could exist in a fully conscious state, in one form or another, without the obligation for dormant, vulnerable, and inattentive sleep.

2. Literature Review

2.1 The history of memory

Memory research has been one of the defining staples of psychological inquiry since the inception of psychology as a discipline in the late nineteenth century. A span of famous psychologists and their theories throughout the last century attests to this. Freud wrote of repressed childhood memories (Freud, 1899). Muller and Pilzecker proposed in 1900 that permanent memory takes time to form, and that during this time, memory remains vulnerable (as reported in Dash, et al., 2004). Pavlov showed that dogs could remember (have a memory for) reinforcing stimuli via associative learning (Pavlov, 1927). Donald Hebb demonstrated in 1949 that novel memory traces must be replayed in their supporting neuronal networks until synaptic plasticity can effect trace consolidation of the memory (Hebb, 1949). In other words, the neurons in the brain that fire together to create a thought make connections with

one another and strengthen this connection every time that specific thought is recreated. The notion that "neurons that fire together, wire together," originates from this work; these connections that are formed are commonly referred to today as Hebbian synapses. In 1956, George Miller concluded that the 'amount' of memory we could work with at any one time was seven 'chunks' of information, plus or minus two. Scoville & Milner (1957) reported the case of patient H.M., the man treated for epilepsy with a bilateral medial temporal lobectomy, who subsequently showed profound anterograde amnesia for new experiences while retaining the memories acquired before the surgery. H.M. could remember events from before the surgery, but was incapable of creating new memories post-morbidity. Finally, Elizabeth Loftus (2003) made a name for herself in the mid-1970's studying the formation of 'false memories' – memory for an event, or misrepresentation of a memory, that is at odds with the reality of what occurred. Loftus' work showed that the veracity of a memory is not as set in stone as we may like to believe it is. Our memories are malleable. Countless other luminaries in the field of psychology have discussed their views on how memories come to be formed and how we use these memories of the past to deal with the reality of the present.

2.2 Types of memory

Memory, as a reference for previous phenomenological experience and as classified in the human animal, can be divided and subdivided into several forms. A glance at the literature will reveal several forms – explicit and implicit, procedural and declarative, episodic, semantic, contextual, short-term, long-term, and working, and several more. These are not exclusive divisions; overlap is possible between many categories of memory. A very general dichotomy can be drawn, however, between two forms of memory – *implicit* or *explicit*.

Implicit memory refers to things that you know, or know how to do, without needing to be consciously aware. One form of this, *procedural memory*, is characterized by the smooth coordination of procedures, such as in riding a bike or playing the piano. While at the beginning you may have to think about all of the procedures you have to do, with training these procedures become fluid. Once you learn a *procedural memory* you can, in essence, forget about it because you no longer need to consciously process the things you need to do – it becomes *implicit.*

Explicit memory refers to things that you know you know. This is sometimes called *declarative memory*, as in, "I declare that I know something." These memories come in several forms. *Episodic memory* is one such form in which you have a personal recollection for an experience. That is, you recall a certain 'what' in a certain 'where' at a certain 'when.' For example, I recall the exact episode for when I formulated the general idea for this proposal – I was driving my Jeep home from the university on Interstate 476 one late day in October of 2005. *Semantic memory* refers to knowledge of the meaning behind a thing (such as facts, names, etc.). If I say 'chair,' you immediately have an idea of what it is that I am sitting on; you have an understanding of the meaning for the word 'chair' that is not necessarily bound to a time or place. *Episodic memories* therefore can entail many *semantic memories* but *semantic memories* do not require episodes. These recollections are explicit. Explicit memory retrieval is believed to be an effortful process, whereas implicit memories are retrieved using relatively automatic processes.

Temporal references can also be appended to memory to describe the duration of time that we have access to the memory. The briefest of these is *working memory*, a term that denotes the bits of memory that we are currently using. Physiologically, this might correspond with neurons in the cortex that are currently firing. These may be memories that are retrieved from the past for current usage, or they may be 'new' memories that have been encoded from sensory perception within the scope of what we are currently engaged in. For example, as I write this paper, my working memory tells me that I have covered all I want to say about it, and that I should proceed with *short-term memory.*

Short-term memory denotes bits of memory that have occurred relatively recently. They are different from *working memories* in that they are not currently being used, but have happened recently enough that they could be recalled. These might be thought of physiologically as traces of activity within the cortex. *Short-term memories* can be forgotten after a length of time if they are not consolidated into what is referred to as *long-term memory.*

Memories deemed to be *long-term* are those that stay with us virtually forever. These are the 'bits' that may have occurred years in the past, but because they have been transferred from a *short-term* into a *long-term* memory, we can retrieve them for use at later dates. These are considered to be physiologically hard-wired neural nets. Connections have been made at the level of the synapse (the area where one neuron

connects to another) that facilitate easy transmission of the memory message.

All of these, it must be admitted, are parameters that have been ascribed to human memory systems. The extent to which animals use these various memory systems is inconclusive. However, that does not mean that memory in animals has not been investigated. A study by Clayton & Dickinson (1998) attempted to display that a type of bird, scrub jays, used *episodic memory* to correctly identify a 'what' and a 'where' food was placed, as well as a 'when' by the fact that one type of food would decay over time. The bird preferentially chose this type of food at first, but preferentially chose the non-decaying food after a time lapse, indicating that it was sensitive to a 'when'. A response study was undertaken by Hampton, et al. (2005) incorporating Rhesus monkeys. Hampton showed that the monkeys displayed a *long-term memory* for the type and location of a food, but not for when they acquired this knowledge. It was contested therefore, that perhaps animals other than humans do not have the ability to form *episodic memories*; perhaps they are 'stuck in time' and can only recall things from the past in the sense that some synaptic connections are stronger than others (that is, some things 'seem' right and other things 'seem' wrong, but the animal does not have a specific episode from the past that it is drawing on to base a decision)(Roberts, 2002). This is not to say that animals are insensitive to time, but that rather, they do not construct episodes of the past. However, ample evidence supports that animals do have a sense of various other types of memory, such as *working, short-term, long-term, and procedural memory.* The mechanisms for *episodic memory* seem to be reserved only for humans. As Tulving points out at the opening of his book, *Elements of episodic memory,* "remembering past events is a universally familiar experience. It is also a uniquely human one." Aristotle would agree.

2.3 The anatomy of memory

Several terms are used to describe the transfer of memory between *working, short-term,* and *long-term* memory. Encoding, consolidation, and retrieval are expressions found throughout the academic literature on memory (Dash, et al., 2004; Dudai, 1996; Siegel, 2001). Encoding refers to the transfer of sensory stimuli into a recognizable phenomenological experience. Consolidation is the transfer of such an experience from the *short-term* to the *long-term,* the stabilizing of a memory. Retrieval is thought of in terms of accessing the *long-term* for use in *working*

memory, a process involving the coordinated reactivation of cortical areas. So far as animals can be shown to learn (via classical condition or operant conditioning), such terms can be applied to many of the creatures in the animal kingdom. An animal would need to encode, consolidate and retrieve the experience to argue that it is learning something in an operant/classical conditioning paradigm.

It should be mentioned here that we have moved away from talk of *implicit memory* and are moving toward forms of the *explicit*. *Implicit memories* have been linked to basal ganglia, cerebellar, and amygdalar structures in the brain, whereas *explicit memories* seem to arise out of the functioning of a loop in the brain that includes the hippocampus, thalamus, and cortex (Mayes, 1995). References to memory from here on will refer to *explicit memory* systems that involved the hippocampal complex.

Consolidation and retrieval of *explicit memory* therefore necessitates the operation of a cortico-hippocampal-thalamic system. The anatomical structures implicated in these memory processes have been investigated and appear to be proximal across a wide range of vertebrate mammals. The anatomy proposed to account for how memory is stored and retrieved draws from a broad sample of studies on structures involved in amnesia, a condition in which memory is selectively forgotten, or more appropriately, in which memories are unable to be consolidated and/or retrieved (Mayes, 1995). The approach used by Mayes (1995) to devise a "memory circuitry," or anatomical interactions that seem to account for memory consolidation and retrieval, was to look at the effects of lesions to several brain structures with regards to amnesia, or loss of memory. Similar to patient H.M. (Scoville & Milner, 1957), studies with rats have revealed that removal of the hippocampus results in temporally graded amnesia (Squire, et al., 2001). Likewise, parahippocampal cortex, perirhinal cortex, and hippocampal lesions all result in amnesia of some form (e.g. retrograde amnesia or anterograde amnesia[1]). Therefore, a circuit in which information flows from the parahippocampal and perirhinal cortices to the hippocampus has been suggested. From the hippocampus, this message is transported to the fornix. From here, the message flows either directly to the anterior nuclei

[1] Retrograde amnesia is a loss of memory for events that occur prior to the onset of the amnesia, as in someone who cannot remember who they are or where they are from. Anterograde amnesia is an inability to learn/remember anything that occurs after the onset of the amnesia, such that you remember everything prior to the event, but cannot remember anything that happened since then other than what is immediately present.

of the thalamus, or indirectly through the mammillary bodies to the thalamus. The thalamus relays the information to frontal lobe regions, such as the retrosplenial and cingulated cortices, and these areas project back onto the perirhinal cortex and parahippocampal cortex, thus completing the loop (see Figure 1). It is hypothesized that *long-term memory* is a result of the parahippocampal cortex and hippocampus essentially replaying the original memory throughout this loop until long-term potentiation takes place and Hebbian synapses form in the cortex. For a limited time, the hippocampus is necessary for memory retrieval.

2.4 Memory consolidation hypotheses

If memory is a result of the aforementioned anatomical structures 'replaying' the original thought processes which leads to the feeling of a memory, the question becomes- how is memory consolidated, how and when does this 'replay' take place? What is the mechanism that makes salient phenomenological experiences reverberate throughout this circuitry so as to be transferred from a vulnerable, transient *short-term memory* into a concrete *long-term memory*? A popular theory that has received much press is that consolidation of recently acquired memory traces requires neuronal replay during REM sleep (Mednick, 2003; Smith, 1995). Indeed, sleep has long been viewed as somehow linked to our memories. As far back as Freud (1899), the dreams that accompanied sleep were said to be the "royal road to the unconscious," our repressed memories and desires. The argument goes that during sleep, a mental inventory of the events from the proceeding day is catalogued as either useful ('keepers') or useless ('forgettable'). The 'keepers' are dreamt about and therefore receive some playback (reverberation through the cortico-hippocampal-thalamic loop), while the forgettable memories are simply ignored and so, therefore, are un-reinforced. This theory was advanced by Francis Crick, who postulated that the primary purpose of REM sleep was the forgetting of unneeded memory traces (Crick & Mitchison, 1983). However, a summary look at sleep patterns among several animals provides contradictory evidence.

Across mammals, sleep electroencephalography (EEG) provides fairly consistent patterns of activity. The normal sleep patterns seen in humans (Non-REM or Slow-Wave-Sleep and Rapid Eye Movement [REM] or Paradoxical Sleep[2]) have been found in nearly every animal

[2]Non-REM sleep is characterized by slow, synchronous firing of neurons in the brain and a drastic reduction of overall activity. It is further subdivided into four stages which demarcate the level of synchronous, pulsating firing that is taking place, and which corresponds to 'how deeply' a person is

investigated, including the platypus (Siegel, et al., 1999), elephant (Tobler, 1992), harp seal (Lyamin, 1993), and dolphin (Mukhametov, 1987).[3] What is interesting to note is that, contrary to what might be expected if the REM sleep-memory consolidation hypothesis were true, humans (which arguably have to learn just as much as any other creature) do not exhibit unusually high amounts of REM sleep (Siegel, 2001). Champion REM sleepers such as the ferret, armadillo, and platypus are not typically described as having superior memories. In contrast, mammals such as bottlenose dolphins and white whales, creatures that have intellectual abilities otherwise found only in humans and in apes, have negligible REM sleep on the order of less than 0.2 hours per day (Siegel, 2001). If REM sleep were necessary for learning, we would not think that dolphins would be such great learners. The alternative hypothesis, which could conceivably account for such sleep patterns across species, is that perhaps the amount of REM sleep that would be required for memory processes varies across phylogeny, and that it is an unreasonable assumption to conclude that a dolphin should need as much sleep as a platypus to learn the same amount of information. However, such an argument suffers from what may be considered an equally unreasonable assumption. Given the lack of empirical data for either stance, the most logical argument will here be followed and the assumption that the amount of REM sleep required for learning should not vary interspecially will be maintained.

Perhaps the correlation that is found between REM sleep and learning is an artifact of the fact that the techniques incorporated in REM deprivation studies cause moderate amounts of stress in the animals and stress by itself impedes memory retrieval (de Quervain, et al., 1998). Many of the REM sleep deprivation studies incorporate the "platform technique" in which an animal is placed on a small platform that is surrounded by water. The premise behind this is that during REM sleep, a complete loss of muscle tone is observed (due to a process that will be described below) that requires the animal to assume a maximally relaxed recumbent posture. Upon doing so, the animal will fall into the water, be startled awake and will resume its post on the platform. NREM sleep is possible during this because the animal does have the muscle tone that can keep it in uncomfortable positions while it enters NREM. The REM-

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asleep. REM sleep is also termed 'paradoxical' because in REM sleep, the brain is just as active, if not sometimes more so, than when we are consciously awake.

[3] For a thorough review, see Campbell & Tobler, 1984, who index the sleep behaviors of over 150 animal species, including invertebrates, fish, amphibians, reptiles, birds, and 14 orders of mammals.

deprived animal has restriction on its motor activity, which has been shown to be stressful. Monkeys that are restricted from moving in a restraining chair develop gastrointestinal ulcers from such stress (Brady, 1958). It is reasonable to assume that the "platform technique" induces some stress in the rat as well. It has been shown that moderate stress, in the absence of any imposed learning task, can produce a marked increase in REM sleep (Siegel, 2001). The converse of this is also true – adequate sleep is needed in order to maintain attention and integrate new material. Just as nutrition, ambient temperature, level of stress, and other factors contribute to our ability to learn and form salient memories, adequate sleep is vital for optimal performance (Siegel, 2001). It would be fallacious, however, to regard REM sleep as the necessary, rate-limiting step in the process of memory consolidation.

While sleep may be highly correlated with learning, it is *non sequitur* to state that sleep is the causal factor for memory consolidation. Perhaps sleep is just providing the necessary time for memories to be replayed in the loop described in Figure 1. Evidence suggests that consolidation of memories in the cortex is a direct result of the frequency with which they are presented (Toppino & Bloom, 2002). Memory improves with repeated exposure, and greater temporally spaced repetitions of a memory appear to help consolidate a memory more so than massed repetitions in immediate succession. To go back to Muller & Pilzecker's theory in 1900 that was referenced earlier, establishing permanent memory takes time. Perhaps sleep provides the 'spacing' needed for permanent memories to be formed.

2.5 The chemistry of memory

A physiological basis for why repeated exposure leads to memory consolidation should also be considered. A review of the biological processes occurring during REM sleep can shed light on this physiological basis.

The key feature of REM sleep is the apparent lack of muscle tone throughout the body, with the exception of the eyes (hence the name: rapid-eye-movement). The mechanism via which this occurs stems from a ramping up of monoamine oxidase (MAO) to prevent the monoamine neurotransmitters of the brain – norepinephrine, epinephrine, histamine, dopamine, and serotonin - from properly functioning. The cells for these neurotransmitters stop discharging completely during REM sleep (Siegel, 2004). Otherwise, we might act out our dreams, as sleepwalkers are wont to do. This is what also gives dreams their sense of 'bizarreness,' as the

areas of the cortex that would normally serve as 'reality checks' do not have the necessary transmitters to relay the message (Rechtschaffen, 1978). Of most importance to the discussion here is the neurotransmitter norepinephrine. Cessation of norepinephrine is linked with reduced expression of several proteins described below, such as *CREB, BDNF*, and *arc* (Cirelli & Tononi, 2000). The expression of these proteins is associated with increased neural plasticity; a decrease therefore would mean a loss of neural plasticity. It follows, then, that we should expect little effect on memory during REM sleep as the chemicals necessary for lasting changes are not active. This is consistent with the rapid forgetting of dreams that are not immediately rehearsed upon waking. The brain, by essentially turning off the 'juice' that helps form lasting memories, prevents itself from rewiring the authentic connections that have been made while awake that might otherwise be inadvertently modified as a result of brain activity during REM sleep.

MAO inhibitors (such as Nardil, Marplan, and Parnate) have been shown to completely suppress REM sleep for as long as treatment with the MAO inhibitor is in use, which may last for years (Siegel, 2001). Millions have taken such drugs without detrimental effect to their memory. Rather, there is actually some evidence that MAO inhibitors improve memory (Vertes & Eastman, 2000). In contrast, pharmacological agents that induce sleep without affecting the amounts of REM versus NREM sleep, such as benzodiazepines, have been noted for their harmful effects on memory (Bixler, et al., 1991; *Physician's Desk Reference*, 2001). This neurochemistry is further evidence that REM sleep is not the mechanism that accounts for memory consolidation.

Briefly, the chemical basis for memory formation will be explained. The formation of *long-term memory* is dependent on both protein synthesis and gene expression (Dash, 2004). These processes are triggered by cascades of cell signaling proteins (e.g. Protein Kinase A [*PKA*], Calcium/Calmodulin-regulated Kinase [*CaMKII*], and Extracellular-signal Regulated kinase [*Erk*]) which work by phosphorylating transcription factors in the cell nucleus, such as the Calcium/cAMP Response Element Binding protein (*CREB*). Phosphorylation of transcription factors in the cell induces the expression of several genes, such as brain-derived neurotrophic factor (*BDNF*), activity-regulated cytoskeleton-associated protein (*arc*), *c-fos*, *zif-268*, and *syntaxin-1B* (Dash, 2004). Such factors are thought to be required for neural plasticity and the formation of *long-term memory*. Several of these

proteins have been shown to increase in the hippocampus shortly after conditioning experiments in mice (Stanciu, et al., 2001). Additionally, *arc* has been reported in the hippocampus soon after the exploration of novel environments (Vazdarjanova, et al., 2002), further lending credence to the notion that these proteins resulting from specific gene expression are correlated with *long-term memory* consolidation.

Recently, it was discovered that memory consolidation is a two-way street. Apparently, consolidation is reversible as well. Reactivation of consolidated memories returns them to a protein-synthesis dependent state (Duvarci & Nader, 2004). The administration of anisomycin, a protein synthesis inhibitor, blocks the reconsolidation of *long-term memories.* In Duvarci & Nader's experimental paradigm, Sprague-Dawley rats were fear conditioned to a stimulus by the administration of an electrical shock, so that they avoided the stimulus at all cost. After acquisition and consolidation of this learned memory, some rats were administered anisomycin and others were administered a placebo. Rats that were injected with anisomycin subsequently forgot the memory in training sessions where the stimulus was presented but the shock was not, whereas rats in the control group maintained their conditioned fear. Facilitation of extinction of the memory via anisomycin was ruled out because reacquisition of the response following anisomycin-induced forgetting resulted in a normal learning curve, as compared with a control group allowed to extinguish their memory over time. The control group showed much quicker renewal.

2.6 Memory retrieval

This leads to some inquiries regarding the flip side of consolidation – memory retrieval.

If memory is stored in a "neurons that fire together, wire together" fashion, we would expect that retrieval of these memories would involve accessing the majority of those same neurons. That is, if cortical activation occurs globally and bilaterally throughout the cortex, it follows that retrieval of the memory for those neuronal activations would involve a global summation of firing neurons. In other words, if in consolidation a memory is distributed throughout the cortex and occurs bilaterally in both hemispheres, then retrieval should require accessing the entire cortex.

Again, sleep research has some critical insights to this conjecture. Aquatic mammals belonging to the orders of *pinnipedia*, *cetacean*, and *sirenia*, display a unique method for achieving quiescent, sleeping

behavior (Tobler, 1995; Oleksenko, et al., 1992; Mukhametov, 1987). The Amazonian dolphin, bottlenose dolphin, pilot whale, porpoise, and sea cow all exhibit unihemispheric sleep patterns in which only one brain hemisphere is somnolent at a time. EEG patterns of one hemisphere will resemble NREM or REM alpha, beta and delta waves (the technical names given to describe the shape and amplitude of waves seen in sleep stages), whereas the other hemisphere will display a typical, theta wave waking pattern (Oleksenko, et al., 1992). The 'awake' hemisphere is active and enables these animals to continuously move, so that they can always come to the surface for air and so that they can continuously swim.

An assumption must be made here that bottlenose dolphins (and the other species mentioned) do form memories of some sort (based upon the fact that they can learn to do tricks and can perform complex maneuvers and jumps with some training). Hypothetically, if a dolphin were to form a memory in one hemisphere only during quiescent, unihemispheric sleep, would it be able to access that memory at a later time when the hemispheres are reversed and the 'memory-containing' hemisphere is asleep? Furthermore, if conflicting memories for the same stimuli existed in opposite hemispheres, how would a dolphin react in a scenario when it encounters the stimuli in a fully, bilaterally-awake state? Simply stated, do dolphins, and by extension other mammals such as humans, retrieve memories in a distributed or localized fashion?

3. Research Proposal

A means to investigate the nature of memory consolidation and retrieval can be garnered from the procedure known as the Intracarotid Amytal Procedure (IAP). The IAP is a test in which first one and then the other cerebral hemisphere is temporarily anaesthetized through direct intracarotid application of sodium amobarbital (Wada, 1949/1997). The carotid arteries are the main passageways in the head and neck that supply blood to the brain. Sodium amobarbital is a barbiturate with sedative and analgesic properties. The IAP (a.k.a. Sodium Amytal Test, amobarbital procedure, or Wada testing) was developed by Juhn Wada in the 1950's as a method for restricting electro-shock convulsions to the non-speech dominant hemisphere of patients with epilepsy in an effort to reduce the effects of electroshock treatment (Van Emde Boas, 1999). Presently, the test is usually performed prior to ablative surgery for epilepsy to gauge the effects the surgery might have. The test is

conducted with the patient awake. Essentially, the anesthetic is introduced into one of the internal carotid arteries via a cannula or intra-arterial catheter. Within seconds this results in a brief and reversible hemiparesis contralateral to the side of the injection. The patient undergoes a neuropsychological assessment, the aim of which is to determine which side of the brain is responsible for certain vital functions including speech and memory. The risk of damaging such structures during surgery can then be assessed using this data.

IAP is routinely applied in the medical field today to determine speech lateralization and for the assessment of memory functions' laterality (Kelley, et al., 2002; Watson, et al., 1998; Rausch, et al., 1989, Rausch, et al., 1984). Effects described from the IAP include motor paralysis of the upper and lower limbs contralateral to the side of the injection (Wada, 1949/1997). Via the use of the IAP, hemispheric dominance for speech, as well as for the memorization of faces, can also be determined (Kelley, et al., 2002). It is interesting to point out here the localized nature of speech. Language function is found to be lateralized in the left hemisphere in 96% of all dextral people (Watson, et al., 1998). Whatever the basis for left and not right hemispheric speech dominance may be, the fact that speech is localized at all is of interest in the consideration of memory retrieval. While speech may be a special case (and an almost exclusively *semantic* form of memory), it nevertheless provides some level of support that memory retrieval may be localized and not pooled in a distributed fashion from all regions of the brain. The question moves then to other kinds of memories: how are they stored and retrieved? When retrieving a memory from the cortex, must we have access to all areas of the cortex that may have been involved, so as to retrieve the memory bit by bit from 'here' and 'there'? Or is it the case that we can use information from just 'here' to recreate the memory?

Given the invasive, and arguable ethicality inherent in doing such an IAP study with human subjects, a research proposal will be suggested that attempts to answer this question using animal subjects. Such questions can be addressed by utilizing the IAP procedure on a monkey trained to operantly respond to stimuli. Since monkeys do not have the complex language system that is found in human beings, the retrieval of other types of memories would have to be investigated. An interval timing paradigm could be used (see Matell & Meck, 2004) in which a monkey is trained to make temporally-guided responses to the onset of a stimulus (i.e. a 4 Hz tone). The monkey is trained that a reward will only be given to the first correct response on a lever after a duration (i.e. 20

seconds) has elapsed. The behavior of the monkey, when represented graphically, gradually approaches a normal, peak-shaped function around the criterion duration. Interval timing represents a good measure to test the nature of memory retrieval because it provides a continuum along which responses can be mapped. A shift in behavior and the ability to respond to a duration at various points along the temporal continuum would serve well to address the nature of memory retrieval.

To test the process for which memory is retrieved, the IAP procedure could be induced to a monkey that is familiar with the nature of its task (i.e. a monkey that has been trained on the interval timing paradigm in the past). It is not envisioned that such pre-training would confound the results of this proposal because the monkey will be exposed to several sessions while under the influence of the IAP until a criterion response rate is met. Pre-training should simply accelerate the rate at which the monkey makes the learning acquisition. Monkeys will be trained, specific to only their left or right hemisphere (counterbalanced between subjects of course), while under the IAP procedure to respond on a lever to a 4 Hz tone after a duration of 20 seconds has elapsed. Monkeys will then be put under the IAP procedure for the opposite hemisphere and will be trained to respond to the same 4 Hz tone on a lever after a duration of 10 seconds has passed. Successive trials, alternating between the two hemispheres would occur, so as to prevent a recency effect during the experimental testing sessions that will follow the training sessions. No evidence of damage is seen in monkeys from proportionally higher doses (than those routinely used for humans) administered in close proximity in time (Van Emde Boas, 1999). Therefore, we can be confident that effects from repeated administration of sodium amobarbital will not develop and confound the results. Thus, at the end of the training sessions, it would be expected that the subject monkeys have either a memory for responding at 10 seconds to a 4 Hz tone in their left hemisphere and a memory for responding at 20 seconds to a 4 Hz tone in their right hemisphere, or vice versa (right hemisphere, 10 seconds; left hemisphere, 20 seconds). Upon reaching criterion for both intervals in the corresponding hemispheres, the monkeys will be allowed to, for the first time, respond to the 4 Hz tone with access to both hemispheres of their brain. Monkey's responses will be observed.

Several outcomes could result from using such a paradigm. If, upon presentation of the 4 Hz stimulus, the monkey responds first at 10 seconds and then again at 20 seconds (a dual peak), this would be indicative of a more localized memory retrieval process, whereas, if the

peak resembles an average of the two initial response rates (i.e. responding occurs around 15 seconds), then a distributed, and somehow integrated memory retrieval process is supported. Hemispheric dominance for the timing of a task will also be considered if the response pattern favors one of the two original response times (e.g. a peak occurring around 17 seconds would support that memory retrieval is distributed, but that the hemisphere trained on a 20 second response interval exerts more dominance for a temporal task than the 10 second trained hemisphere.)

As an aside, it will be interesting to note if there appears to be hemispheric differences among the experimental groups. There are several articles that point to hemispheric dominance in the ability to interval time that could support an outcome that favors a left-dominant or right-dominant hemisphere for interval timing. As such, some theories contend that the left hemisphere is primarily responsible for our sense of time, whereas other theories suggest that the right hemisphere is the basis for this ability. Koch et al. (2002) proposed that right dorsolateral prefrontal cortex (DL-PFc) lesions, but not left DL-PFc lesions alter subjects' accuracy of reproduction of subjective time, whereas Binkofski and Block (1996) reported leftward shifts in response time following left DL-PFc lesions. Matell, et al. (2000) also reports that lesions of the left, but not right substantia nigra pars compacta (SNPC) produce deficits in the temporal control of responding to an interval. Therefore, it will be interesting to see if hemispheric differences amongst the experimental groups arise.

In any event, it is believed that the proposed experiment would provide an adequate means to investigate the nature of the process of memory retrieval. Some considerations should be made, however, regarding such a procedure that could limit the effectiveness of this experiment. It is unknown how long monkeys would need to be subjected to training under the IAP for a learning acquisition curve to be enacted. While it is not foreseen that the pharmacokinetic and pharmacodynamic effects of sodium amobarbital would be an issue in the short run, this is not to say that some effects wouldn't appear after repeated sessions. In typical interval timing training paradigms using rats, the animal is subject to two to three weeks of training sessions that last two hours per day. The IAP procedure only has effects that last for roughly three minutes before the drug starts to wear off. Therefore, the first two minutes after the injection of sodium amobarbital would be the critical window during which training would take place. Training would have to terminate then

so as to prevent the anesthetized hemisphere from recovering and getting a hint at what the other hemisphere is doing/learning. As mentioned earlier, several trials could be issued on the same day. One just must be cognizant of the time parameters for individual sessions. If learning acquisition takes many, many days, it is conceivable that some type of pharmacological dependence could develop with the interaction of the barbiturate sodium amobarbital. Again, that is why monkeys with a history of interval timing training would be desired, so that pace of learning acquisition is accelerated.

The second consideration that some may consider is the transfer of the memory between hemispheres during non-training. This is not believed to be an issue from the author's perspective because of the nature of memory. Memory is often thought of as a *thing*; some*thing* gets encoded; some*thing* is consolidated and retrieved. *Something* is tossed back and forth around the brain and the little homunculus in the head is searching for this *thing* when he is trying to find a memory. This is the wrong way to view memory however. Memories are not 'items' sent down from cortical areas to the hippocampus and 'stored' there temporarily until they can be transferred back to the cortex as a concrete long-term memory. Rather, creating a memory is more of a process of reinforcement – positive feedback loops that reverberate via the hippocampal complex throughout the cortex, strengthening the synapse that were active during a perception to the point that the flow of information is facilitated through these connections easily and quickly. Memory becomes an emergent property of this feedback loop. It would seem intuitive that if something like language is primarily located in our left hemisphere, and temporary loss of language is seen as a result of the anesthetization of that hemisphere, then transfer of the memories for speech between the hemispheres is unlikely to be occurring. Otherwise, the right hemisphere (non-speech dominant hemisphere) would be able to compensate when the left hemisphere is anesthetized. The transfer of other memories between hemispheres after being trained unihemispherically on the IAP procedure seems dubious.

So, why do many studies implicate sleep with memory processes? Perhaps it is in fact due to a physiological mechanism that emerges out of sleep. During REM sleep the brain is as active as during the waking state (Siegel, 2001). However, during non-REM sleep, especially during the delta rhythm, slow-wave sleep described in Stages 3 and 4, the action potentials of the brain are firing in synchronicity. Slow pulses reverberate throughout the brain. It is conceivable that this slow-wave sleep, and the

reverberation seen, is of a similar nature to the reverberation of memory processes throughout the hippocampal complex. There is some evidence that it may be this non-REM sleep that is most critical for memory formation (Ribeiro, et al., 2004). If this is the case, it is not necessarily the sleep that is needed for memory formation; it is the process of decreased cortical activity that allows for reverberation to take place. As such, quiescent states of consciousness, such as meditation might also suffice for memory formation.

That is another investigation and will be reserved for another time. However, it does raise an interesting conjecture or two about the possibility of an evolutionary drive in humans *for* sleep deprivation. Theoretically, if alternative mechanisms could replicate those deemed to be necessary for the optimal acquisition of memory and the preservation of attention that is garnered from sleep, then it would make sense to make use of such mechanisms instead of giving way to sleep, a state of consciousness in which we are vulnerable and inattentive to the outside world. If mammalian creatures such as the dolphin and the whale, as well as several avian species such as the mallard, domestic chicken, blackbird, and domestic pigeon (Rattenborg, et al., 2000) have adapted a process by which they can avoid the defenseless state that is entered when sleeping bihemispherically, then it is conceivable, and perhaps even desirable that humans might be able to operate in similar fashion as well.

3. Bibliography available online at www.publications.villanova.edu/CONCEPT

4. Figure Captions

Figure 1. Cortico-hippocampal-thalamic loop. The brain structures implicated in memory consolidation are represented here in a graphical flow chart. Perceptions from the frontal and parietal cortices enter into the parahippocampal and perirhinal cortices of the temporal lobe. From here, information is passed through the hippocampus, to the fornix. It then goes directly to the thalamus or indirectly there via the mammilary bodies. Finally, information is passed back to the frontal lobes via the retrospenial cortex and the cingulated cortex.

Figure 1. Cortico-hippocampal-thalamic loop.